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ORIGINAL ARTICLE

Sperm Cryopreservation Outcomes in Transgender Adolescents Compared with Adolescents Receiving Gonadotoxic Therapy

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Abstract

Purpose: The target population for fertility preservation recently has been expanded from adolescents with cancer undergoing gonadotoxic chemotherapy to include transgender youth before initiating gender-affirming hormone therapy. Patients and providers may have knowledge deficits regarding options for fertility preservation, accessibility, and feasibility of its techniques, and impact of treatment on future fertility. This study describes outcomes of sperm cryopreservation in transgender male-to-female (affirmed female) youth and compares semen parameters with adolescents diagnosed with cancer.

Methods: Medical records of transgender-affirmed female adolescents and adolescent males diagnosed with cancer who underwent sperm cryopreservation at the Fertility and Advanced Reproductive Medicine clinic of the University of Texas (UT) Southwestern Medical Center between March 2015 and March 2020 were reviewed. Demographic data were recorded and values for sperm parameters (volume, count, total count, motility (%), total motile) were collected. When available, hormone levels (luteinizing hormone, follicle-stimulating hormone, testosterone, and estradiol) and Tanner stages were also assessed. The two populations were compared using chi-square analysis and two-sample student's *t*-test. Data are presented as mean ± standard deviation.

Results: While semen quality parameters trended lower in transgender youth compared with adolescents with cancer, there was no statistically significant difference between groups. While four out of 18 patients in the transgender group had azoospermia, mean semen quality parameters fell within normal adult reference ranges for both groups.

Conclusion: Sperm cryopreservation for transgender youth and adolescents with cancer is feasible, inexpensive, and does not result in significant treatment delays. This information can improve counseling and access to these procedures, particularly in the transgender population.

Keywords: affirmed female; fertility preservation; sperm cryopreservation; transgender

Introduction

The target population for fertility preservation techniques was historically children and adolescents with cancer undergoing gonadotoxic treatment. This intended group now includes transgender children and adolescents before initiating hormonal transition and undergoing gender-affirming surgery. For both male patients with cancer and transgender male-to-female (affirmed female) patients undergoing hormonal transition with gender-affirming hormone therapy (GAHT), sperm cryopreservation is an option that is now available at most fertility centers. Cryopreserved sperm has good survival rates using modern processing techniques and its use enables patients to have genetically related offspring in the future.[1]

Prolonged use of cross-sex hormones can make biological reproduction difficult for transgender patients.

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Preliminary data were presented as a poster presentation at the ACOG Annual Clinical and Scientific Meeting, Nashville, Tennessee, May 2019, titled "Comparing Semen Quality Parameters in Adolescents with Gender Dysphoria with Adolescents undergoing Gonadotoxic Therapy." The preliminary data were also presented at departmental grand rounds Department of Obstetrics and Gynecology at UT Southwestern Medical Center in Dallas, Texas, in January 2019.

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Options for fertility preservation for affirmed female patients include sperm cryopreservation, electroejaculation, or testicular sperm extraction.[2] A recent systematic review claims that fertility preservation counseling for transgender adolescents should begin as early as possible to allow time for informed decision making.[3] The World Professional Association for Transgender Health and the American Society for Reproductive Medicine both consider discussing goals for future fertility and options for fertility preservation as the standard of care for transgender individuals before initiation of gender-affirming hormones.[4,5]

Abnormal semen parameters in adults who underwent sperm cryopreservation during gender-affirming therapy have been reported, including motility and morphology.[6,7] However, the data in adolescents are limited. The Endocrine Society recommends starting gender-affirming therapy by the age of 16, and as early as the age of 14 under compelling circumstances.[8] While some evidence suggests that interest in parenting biological children is lower among transgender youth, it is undetermined whether attitudes will change over time.[9] This underscores the need to address the dearth of information on outcomes of fertility preservation procedures in transgender adolescents.

This study aims to describe outcomes of sperm cryopreservation in adolescent transgender-affirmed females at our institution and compare sperm parameters with adolescent males diagnosed with cancer during the same time period. The end goal is to demonstrate the feasibility of sperm cryopreservation in the transgender population to expand patient counseling and access to these procedures.

Materials and Methods

The GENECIS (GENder Education and Care, Interdisciplinary Support) program at Children's Health in Dallas, Texas, provides affirmative, comprehensive endocrine care, and mental health support for transgender youth. The clinic offers sperm cryopreservation for fertility preservation in conjunction with the Fertility and Advanced Reproductive Medicine clinic at the University of Texas (UT) Southwestern Medical Center. Sperm cryopreservation is offered to oncology patients from Children's Health at the same fertility clinic.

Medical records of transgender-affirmed female adolescent patients and adolescent male patients with a diagnosis of cancer who underwent sperm cryopreservation at the Fertility and Advanced Reproductive Medicine clinic of the UT Southwestern Medical Center between March 2015 and March 2020 were reviewed. Patients, age 13–20, were considered for inclusion. For the affirmed female patients, cryopreserved sperm samples were obtained before initiating puberty suppression and/or GAHT. All samples in this study were collected through ejaculation. Patients with prior exposure to gonadotropin-releasing hormone agonist for puberty suppression, estrogen, or spironolactone, were excluded from the study.

For adolescent males diagnosed with cancer, sperm was collected before treatment with chemotherapy and radiation. Demographic data were recorded and values for sperm parameters (volume, count, total count, motility (%), and total motile) were collected. When available, blood hormone levels (luteinizing hormone, follicle-stimulating hormone [FSH], testosterone, and estradiol) and Tanner stages were also collected. Data from the two populations were compared using chi-square analysis and two-sample Student's *t*-test. Data in tables are presented as mean ± standard deviation (SD).

Results

A total of 45 adolescents were included in the study. Of the 45 patients included, 18 were transgender-affirmed female adolescents and 27 were adolescent male cancer patients. If a patient had multiple collections, only the first sperm sample was used in the analysis (Supplementary Tables S1 and S2). The demographic characteristics are shown in Table 1. All patients had documented Tanner stages of IV or V. There were no statistically significant differences in age, height, weight, and body mass index.

Sperm parameters for both groups are shown in Table 2.[10] All parameters trended lower in transgender youth in comparison with adolescent males with cancer, but there were no statistically significant differences between groups.

Table 1. Demographic Characteristics

	Transgender female adolescents ($n=18$)	Male adolescents with cancer ($n=27$)	p
Age (years)[a]			
Mean	15.8 (±1.6)	16.4 (±1.8)	0.2
Minimum	13	14	
Maximum	18	20	
Height (cm)[a]	174.1 (±7.1)	173.7 (±6.8)	0.9
Weight (kg)[a]	78.0 (±23.3)	76.1 (±17.9)	0.8
BMI (kg/m^2)[a]	25.6 (±6.7)	25.4 (±6.5)	0.9

[a]Samples were compared using two-sample Student's *t*-test.
BMI, body mass index.

Table 2. Sperm Parameters in Transgender Female Adolescents and Adolescent Males with Cancer[a]

	Transgender female adolescents	Male adolescents with cancer	*p*	Adult normal range
Volume (mL)	1.66 (±1.12)	2.10 (±1.43)	0.30	≥1.5
Concentration (million/mL)	44.8 (±50.3)	47.8 (±55.4)	0.85	≥15
Total count (million)	76.7 (±118.9)	84.9 (±99.4)	0.81	≥39
Motility (%)	43.1 (±24.6)	44.9 (±22.7)	0.81	≥40
Total motile (million)	43.0 (±64.7)	48.5 (±62.1)	0.78	N/A

[a]Samples were compared using two-sample Student's *t*-test.
N/A, not applicable.

Of note, four out of 18 affirmed female patients (22.2%) were noted to have sperm counts of zero (azoospermia) despite reported Tanner staging of at least IV. These patients had prepubertal gonadotropin levels and had no prior ejaculatory emissions. Gonadotropin, testosterone, and estradiol levels obtained before initiation of puberty suppression and/or GAHT in the transgender-affirmed female patients are shown in Table 3.[11]

Discussion

This is the first study to describe sperm quality in transgender adolescents, as well as to include a comparison with age-matched peers diagnosed with cancer before gonadotoxic therapy. Sperm of transgender-affirmed female adolescents showed trends for lower quality parameters than their oncology counterparts despite similar ages, Tanner stages, and other anthropomorphic measurements, although there was no statistically significant difference between groups. The semen quality parameters for both groups in the study fall within the normal adult reference ranges revised by the World Health Organization in 2010. While the four patients with azoospermia in the transgender group raise concerns, the findings overall demonstrate the feasibility of fertility preservation for most patients in these groups.

Table 3. Gonadotropin and Gonadal Sex Hormone Blood Levels in Transgender-Affirmed Female Adolescents Before Initiation of Puberty Suppression and/or Gender-Affirming Hormone Therapy

	Transgender female adolescents, mean (*n*)	Adult male reference ranges
LH (mU/mL)	2.18 (13)	0.9–10.6
FSH (mU/mL)	2.31 (13)	1.6–17.2
Testosterone (ng/dL)	344.6 (14)	162–845 (Tanner stage IV–V)
Estradiol (pg/mL)	20.8 (13)	7.6–42.6

FSH, follicle-stimulating hormone; LH, luteinizing hormone.

There is limited data regarding semen analysis parameters for healthy adolescents in the literature, as semen analyses are rarely performed for young patients outside of the context of fertility preservation. Before cross-sex hormone or gonadotoxic cancer treatment, semen analysis parameters for the majority of patients in both transgender adolescents and adolescent groups with cancer fall within the reference ranges established for adults.

Halpern et al. described azoospermia in 8.6% (17 out of 197) of adolescents with cancer presenting for fertility preservation, and a decline in prevalence of azoospermia with increasing age.[12] Azoospermia has also been previously reported in transgender women. In one cohort of 260 affirmed female women between ages 16 and 52, 21 patients (8.1%) had azoospermia.[13] Three of the 21 azoospermic patients had used hormone therapy before semen collection, but all had been off of treatment for a minimum of 3 months and no correlation between past hormone use and lower semen parameters was seen.[13] Azoospermia was still observed after 6 months off of hormone treatment.[13] Endocrine evaluations of the three azoospermic women were all in the normal range, with the exception of one FSH value, which was elevated to 15.7 U/L.[13]

Our study has a higher percentage of azoospermia in the transgender female group (22.2%) than what was described in cancer patients and transgender patients in the above studies.[12] Azoospermia in the transgender group in the present study is a clinically significant finding that should be discussed in patient counseling before undergoing fertility preservation. While the patients with azoospermia had Tanner IV staging documented in consultation notes before fertility preservation, due to the retrospective nature of the study, the Tanner staging could not be confirmed for accuracy for each patient.

The other study describing azoospermia in affirmed female women states that decreased semen quality could not be explained by abnormal endocrine laboratory results, previous GAHT, history of cryptorchidism or inguinal hernia repair, and history of anxiety or depression.[13] Hypothetical explanations for lower semen quality offered include low frequency of masturbation, gender-affirming hormone use, keeping genitals tight against the body, or bringing the testicles into the inguinal canal; still, the authors conclude there is no clear explanation for the impaired semen quality in the cohort.[13] Etiology in one case report was not elucidated due to small sample size and lack of complete

laboratory results and clinical data known to influence semen quality.[14]

The mean semen parameters for both cancer patients and affirmed female patients fell within normal ranges for healthy adults. Another case report highlighting 27 transgender women shows mean semen quality parameters overall similar to the ones described in this study for transgender individuals (mean concentration 46.9 million/mL, mean motility 42.9% in the study by Hamada et al.; and 44.8 million/mL, mean motility 43.1% in the affirmed female patients in the present study).[14]

These robust mean values are perhaps surprising to some readers, as physical illness such as cancer and infection are recognized to harm sperm production. Also, transgender adolescents are often afflicted with comorbid mood disorders and stress, which can affect reproduction. High levels of stress in couples have been linked to *in vitro* fertilization failures,[15] and stress and everyday life factors have been associated with sperm DNA damage in adult men.[16] On the other hand, a recent review states that previous literature has not shown any association between self-reported stress or stressful life events and decreased testicular function.[17] It is unclear if the emotional and physical stress that transgender and cancer patient groups experience could have an effect on their semen parameters.

Given the small sample size in this series, more information is needed to evaluate the effects of varying degrees of stress and illness on sperm quality. The gonadotropin levels measured in the affirmed female patients were at the lower end of normal for the adult male reference ranges[11]; one possible explanation of this is an underdeveloped hypothalamic–pituitary–gonadal axis in transgender adolescents. More data are needed to better assess trends in hormone levels compared with normal adults, as fewer than half of transgender patients included had hormone levels measured.

The semen analyses included in this study were evaluated before initiating gender-affirming hormonal transition. Adeleye et al. showed that sperm collected from transgender female patients while on hormonal medication have markedly abnormal semen parameters, including concentration, progressive motility, and total motility.[6] There is limited data examining threshold length of time of cross-sex hormone treatment that causes infertility. Counseling patients and their families on the appropriate timing of sperm cryopreservation before hormonal transition remains an important feature of patient education.

The limitations of this retrospective analysis include its small study population. As a result, the data did not achieve statistical significance comparing the two groups. It is unclear if this is because the groups are similar, or if the differences are not large enough to detect a difference. More patients are needed to increase the power and better characterize differences, if they are indeed present. Given the retrospective design, demographic factors that could be confounders also impacting semen parameters were not available for evaluation. These include medications, lifestyle considerations (such as smoking and substance abuse), and prior sexual activity or ejaculatory emissions.

Conclusion

We sought to gather information about fertility preservation outcomes in transgender youth to expand recommendations for patients and their parents. This group has traditionally received infrequent counseling about fertility options.[18] Whether or not one pursues fertility preservation hinges on provider knowledge, patient and parent opinions, and availability, which can vary widely between institutions and geographic areas. This study supports the feasibility of sperm cryopreservation in the adolescent population, and assures that sperm cryopreservation does not significantly delay initiation of GAHT.

While the mean values for both cancer and transgender patients fell within range for normal male adults, the SDs were rather large and four of 18 transgender patients had azoospermia. Oligospermia or azoospermia in cancer patients and transgender females may affect utility of cryopreserved sperm, and consultation with a fertility specialist will guide the optimal number of vials to freeze depending on one's future goals.[19] Exploring the mechanisms responsible for the azoospermia seen in affirmed females is a possible future direction of research. Future investigations aim to include prospective information about reproductive choices of transgender-affirmed females with history of sperm cryopreservation, and pregnancy and live birth outcomes to support that genetically related offspring is achievable for this population.

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Ethics Exemption

This study was granted exemption by the Institutional Review Board of UT Southwestern.

Author Disclosure Statement

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Supplementary Material

Supplementary Table S1
Supplementary Table S2

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Abbreviations Used

BMI = body mass index
FSH = follicle-stimulating hormone
GAHT = gender-affirming hormone therapy
LH = luteinizing hormone
N/A = not applicable
UT = University of Texas